

OTHER CLINICAL STUDIES

Is Cortisol Involved in the Alcohol-Related Fat Mass Impairment? A Longitudinal Clinical Study

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Abstract — Aims: Subjects with chronic alcohol abuse can present several metabolic and nutritional alterations. The hypothalamic-pituitary-adrenal (HPA) axis may play a role in these nutritional and metabolic disorders. The goal of this study was to investigate if there is any relationship between HP-hormones and metabolic and nutritional parameters in alcoholic subjects. **Methods:** Sixteen alcoholics were considered before and after 3 months of total alcohol abstinence. HP-related hormones were determined. Nutritional and metabolic parameters were assessed by dual-energy X-ray absorptiometry (DXA) and indirect calorimetry. **Results:** At baseline, a significant negative correlation was found between fat mass (FM) and cortisol ($r = -0.54$, $P = 0.03$). During abstinence, a significant increase of both body mass index (BMI) ($P < 0.0001$) and FM ($P < 0.0001$) was found at 12 weeks compared to baseline. A significant decrease of both plasma cortisol ($P = 0.044$) and aldosterone ($P = 0.023$) was found at 12 weeks compared to baseline. At 12 weeks, the significant correlation between cortisol and FM disappeared. **Conclusions:** A higher HPA-axis activation—reflected by higher cortisol levels—was associated with a lower FM in alcoholics. Conversely, during total abstinence a reduced HPA-axis activity can play a role in the parallel nutritional recovery. The present results suggest a role of the HPA axis throughout cortisol both in the etiology of the alcohol-related nutritional alterations and in their recovery after a period of total alcohol abstinence.

INTRODUCTION

Among the alcohol-related diseases, nutritional disorders and alterations of body composition represent important medical problems (Lieber, 1995; Addolorato, 1998). For example, studies performed in our laboratory showed the presence of several metabolic and nutritional alterations in alcoholic patients, as a high resting energy expenditure (REE) (Addolorato *et al.*, 1997a), a preferential utilization of lipids as an energy substrate (Addolorato *et al.*, 1998b) with related reduction of the fat mass (FM) (Addolorato *et al.*, 2000), and an alteration of the body fluid distribution (Addolorato *et al.*, 1999). These data have also been confirmed by other investigators (Glória *et al.*, 1997; Levine *et al.*, 2000; Santolaria *et al.*, 2000). This alcohol-related impairment seems to be specific of patients with chronic alcohol abuse since healthy subjects consuming moderate amounts of ethanol do not show significant alterations of the nutritional status and body composition (Addolorato *et al.*, 2008). The most severe malnutrition is accompanied by a significant reduction in muscle mass (Lieber, 2003) and an alcohol-induced muscle disease has also been described as a result of a chronic alcohol ingestion (Preedy *et al.*, 2003). The most severe malnutrition is generally found in those alcoholics who are hospitalized for medical complications of alcoholism (e.g. alcohol-related liver disease or other organ damage) (Lieber, 2003). Heavy drinkers not requiring hospitalization for alcohol-related medical problems, in contrast, often are not malnourished (Feinman and Lieber, 1998). In these people, drinking, especially when accompanied by a high-fat diet and lack of physical activity, may actually lead to obesity of the trunk of the body (Lieber, 2003). A recovery of the impaired nutritional status in alcoholics has been reported after at least 3 months of total alcohol abstinence (Addolorato *et al.*, 1998a). Chronic ethanol abuse is able to induce functional alterations

of the microsomal ethanol-oxidizing system (MEOS) and mitochondria throughout the increase of free radicals production (Addolorato, 1998). Alcohol abstinence is able to recover these alterations by a decreased free radicals production (Addolorato *et al.*, 1997b; Sastre *et al.*, 2007) and consequently by the restoration of the MEOS and mitochondrial systems (Addolorato *et al.*, 1998a). Our laboratory had hypothesized that the nutritional impairment present in alcoholics could also be related to the activation of the hypothalamic-pituitary-adrenal (HPA) axis with the consequent increase of corticoids (Addolorato *et al.*, 1998a). Consistent with this hypothesis, a reduced HPA activity during abstinence and the consequent reduced corticoids could contribute to the recovery of the nutritional impairment. This hypothesis is consistent with the known impairment of the HPA axis in subjects with chronic alcohol abuse. In fact, alterations in the HPA axis in alcoholism have been described, including an ethanol-induced HPA-axis injury in actively drinking alcoholics (Wand and Dobs, 1991) and an impaired hypothalamic and pituitary responsiveness in recently withdrawn chronic alcoholics (Costa *et al.*, 1996). Furthermore, a relatively high dose of alcohol taken orally is able to produce an increase of cortisol that is smaller in heavy drinkers compared to light drinkers (King *et al.*, 2006). The reduced cortisol reactivity in the heavier drinkers is consistent with the evidence that individuals at risk for alcoholism are hyporesponsive to physical and psychological stress (King *et al.*, 2006). Moreover, it has been suggested that acetaldehyde, rather than ethanol *per se*, may be responsible for direct adrenal stimulation by alcohol (Cobb and Van Thiel, 1982). This is consistent with the observation of decreased cortisol levels following intravenous alcohol infusion (Ray *et al.* 2009).

The present study was planned to test the hypothesis of a role of the HPA axis in the nutritional impairment present in actively drinking alcoholics. In particular, since obviously the

HPA axis is part of the hypothalamic-pituitary (HP) axis, both corticoid hormones and other HP and HP-related hormones were assessed. Their relationship with body composition and nutritional assessments was investigated.

SUBJECTS AND METHODS

Subjects

Data from a protocol assessing the relationships between alcohol craving and hormones were utilized (Leggio *et al.*, 2008a, 2008b). Briefly, 80 patients diagnosed with alcohol dependence using DSM IV criteria (American Psychiatric Association, 1994) and referred to our Alcoholism Treatment Unit of the Institute of Internal Medicine (Catholic University of Rome, Italy) from June 2006 to February 2007 were consecutively considered for eligibility for the study after giving written informed consent. The protocol complied fully with the guidelines of the Ethics Committee of the Università Cattolica del Sacro Cuore (Rome, Italy). Patients considered for further analysis were active drinkers with an alcohol intake over 80 g of ethanol/day during the 24 h before the admission day (baseline). The following exclusion criteria were applied: a current axis 1 psychiatric diagnosis on DSM-IV other than alcohol or nicotine dependence; a history in the last 6 months of substance abuse or dependence, not including dependence on alcohol or nicotine; alcoholic hallucinosis; moderate or severe alcohol withdrawal syndrome requiring a pharmacological treatment according to the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale (Sullivan *et al.*, 1991); epilepsy; obesity, diabetes mellitus and/or metabolic syndrome; impaired lipid metabolism; hypoalbuminemia; severe liver, pancreatic, kidney, and/or cardiovascular impairment; all the endocrine disorders; neoplastic diseases; subjects that were pregnant or lactating; use of drugs potentially influencing metabolism and/or endocrine system and/or alcohol craving; major surgery; caloric deprivation; psychological stress; fever and/or intense physical activity. A total of 25 actively drinking alcohol-dependent patients satisfied the inclusion/exclusion criteria and were initially considered for the study. Blood samples were tested at the admission day (baseline). No medication was administered before blood collection. Patients were then included in a multidisciplinary treatment program to achieve and maintain abstinence from alcohol, including psychological support counseling, self-help groups and baclofen administration. Baclofen was chosen as the drug treatment based on the previous research by our laboratory (Addolorato *et al.*, 2002, 2007). Patients were checked as outpatients every 2 weeks. During the 12-week treatment, 5 (20%) patients dropped out and 4 (16%) relapsed. The remaining 16 patients showing total alcohol abstinence (age: 42.25 ± 6.3 years; males: 62.5%; daily alcohol intake: 288.75 ± 84.1 g; duration of alcohol dependence 13 ± 8 years) were considered for the analysis. Their alcohol abstinence was confirmed by self-reported alcohol intake, family member interview, determination of blood alcohol concentration and significant reduction of markers of alcohol abuse [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT) and mean cellular volume (MCV)] (Table 1).

Table 1. Blood markers of alcohol abuse in the alcoholic patients enrolled in the present study

	Baseline	At 12 weeks
AST (UI/L)	93.75 ± 113.6	$57.2 \pm 84^{\dagger}$
ALT (UI/L)	92 ± 109.3	$59 \pm 88.3^{\dagger}$
GGT (UI/L)	202.2 ± 262	$64.5 \pm 127.1^{\dagger}$
MCV (fl)	95.5 ± 9.1	$91.5 \pm 7.2^{\dagger}$

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; MCV, mean cellular volume.

$^{\dagger}P < 0.05$: 16 abstinent alcoholic patients at baseline versus at 12 weeks.

Methods

Hormonal determinations and nutritional measurements were performed both on the day of admission (baseline) and on the 12th week of treatment.

Hormonal determinations. Blood samples were collected at about 8 a.m. after an overnight food fast and hormone determinations were performed by standardized techniques. Specifically, the hormonal assessment included (i) the HP-hormones: adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), prolactin (PRL), growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH); and (ii) the HP-related hormones cortisol, aldosterone, renin, natriuretic peptide (namely, N-terminal pro-B-type natriuretic peptide: NT-proBNP), free triiodo-thyronine (free-T3) and free thyroxine (free-T4).

Nutritional measurements. Body weight was measured to the nearest 0.1 kg with a beam scale, and height was measured to the nearest 0.5 cm with a wall-mounted stadiometer while the subjects were wearing light clothes and no shoes. Body mass index (BMI) was computed as the ratio between body weight (kg) and height (m^2). In order to determine the FM and the fat-free mass (FFM), body composition was assessed by dual-energy X-ray absorptiometry (DXA), using a whole body densitometer (Lunar DPX-L, Madison, WI, USA; software version 3.65), as previously described (Capristo *et al.*, 2000; Addolorato *et al.*, 2006; Malandrino *et al.*, 2008; Leggio *et al.*, 2008c). Total body water (TBW) was calculated assuming that 73.2% of FFM is TBW, as previously reported (Addolorato *et al.*, 1999). Respiratory gas exchange measurements were performed over 60 min by continuous indirect calorimetry with an open-circuit ventilated-hood system (Deltatrac, Datex Instrumentarium Corp, Helsinki, Finland) under strictly standardized conditions, as previously described (Capristo *et al.*, 2000; Addolorato *et al.*, 2006; Malandrino *et al.*, 2008; Leggio *et al.*, 2008c). REE and non-protein respiratory quotient (npRQ) were calculated from oxygen consumption, carbon dioxide production and nitrogen urinary excretion, as previously described (Addolorato *et al.*, 1998b). The values of REE measured by indirect calorimetry were compared with the theoretical values of basal metabolic rate (BMR). BMR was calculated by the Harris-Benedict equations (Harris and Benedict, 1919).

Statistical analysis. The values were expressed as mean \pm standard deviation and categorical data as percentage. The normality of data distribution was tested by the Kolmogorov-Smirnov test and when abnormal, the data were log transformed. Pearson correlation coefficients were used to test the correlations among data analyzed. The paired sample *t*-test

Table 2. Body composition and metabolic variables in the alcoholic patients enrolled in the present study

	Baseline	At 12 weeks
Weight (kg)	67.3 ± 13.4	68.6 ± 13.4 [§]
Height (cm)	170.1 ± 7.5	170.1 ± 7.5
BMI (kg/m ²)	23.1 ± 3.9	23.5 ± 3.8 [§]
FFM (kg)	51.3 ± 8.1	51.4 ± 7.9
FM (kg)	16 ± 8.9	17.2 ± 9.2 [§]
TBW (L)	37.5 ± 5.9	37.6 ± 5.8
npQR	0.7 ± 0.6	0.7 ± 0.1
REE (kcal/day)	1800 ± 442	1600 ± 251 [§]
BMR (kcal/day)	1510 ± 214	1530 ± 212

BMI, body mass index; FFM, fat-free mass; FM, fat mass; TBW, total body water; npQR, non-protein respiratory quotient; REE, resting energy expenditure; BMR, basal metabolic rate.

[†] $P < 0.0001$ versus 16 alcoholic patients at time T0.

[§] $P < 0.05$ versus 16 alcoholic patients at time T0.

was used to compare subjects at baseline and at 12 weeks. The *a priori* limit for statistical significance was $P < 0.05$.

RESULTS

Nutritional (weight, height, BMI, FM, FFM, TBW) and metabolic (npRQ, BMR, REE) parameters at baseline and at 12 weeks are reported in Table 2. All the hormone values were in the normal range both at baseline and after 12 weeks of abstinence (data not shown). At baseline, a significant negative correlation was found between FM and cortisol ($r = -0.54$, $P = 0.03$) (Fig. 1a). The FFM positively correlated with free-T3 ($r = 0.53$, $P = 0.035$) and free-T4 ($r = 0.53$, $P = 0.033$). The free-T4 positively correlated with the REE ($r = 0.63$; $P = 0.009$). During abstinence, a significant increase of both BMI ($P < 0.0001$) and FM ($P < 0.0001$) and a significant reduction of REE ($P = 0.015$) were found at 12 weeks compared to baseline. A significant decrease of both plasma cortisol ($P = 0.044$) and aldosterone ($P = 0.023$) levels, a significant increase of renin ($P = 0.037$) and a trend toward a significant increase of the NT-proBNP ($P = 0.053$) were found at 12 weeks compared

to baseline. No significant changes in the plasma levels of the other hormones evaluated (TSH, fT3, fT4, PRL, FSH, LH, GH and ACTH) were found. At 12 weeks, the significant correlation between cortisol and FM disappeared (Fig. 1b). Free-T3 showed a significant positive correlation with both FFM ($r = 0.73$; $P = 0.001$) and TBW ($r = 0.74$; $P = 0.001$). Free-T3 also correlated positively with REE ($r = 0.66$; $P = 0.006$). NT-proBNP showed a significant negative correlation with both FFM ($r = -0.59$; $P = 0.016$) and TBW ($r = -0.59$; $P = 0.016$). No other correlations were found between hormones and nutritional parameters both at baseline and at 12 weeks.

DISCUSSION

This study showed the presence of a significant inverse correlation between FM and blood cortisol level during the active-drinking phase but not after 12 weeks of alcohol abstinence in alcohol-dependent subjects. This study also showed that body composition seems to be indirectly related to the HP axis, in other words via the hormones produced peripherally by the adrenal (i.e. cortisol and aldosterone) and thyroid (i.e. free-T3) glands. In contrast and consistent with this observation, body composition parameters were never correlated with the central pituitary hormones, namely ACTH, PRL, GH, TSH, FSH and LH.

This study demonstrated a negative correlation between blood cortisol levels and FM in alcoholics in the active-drinking phase. This correlation disappeared after 3 months of total abstinence. Also, after 3 months of abstinence, a significant increase of FM and a significant reduction of both cortisol and aldosterone were observed. All together, these results demonstrated the hypothesis previously performed by our group (Addolorato *et al.*, 1998b) that the activation of the HPA axis could play a role in the nutritional impairment present in alcoholics. This is supported by the negative correlation between cortisol and FM. It has been described that cortisol has two apparently opposed effects since cortisol is known to increase whole body lipolysis while chronic hypercortisolemia results in increased

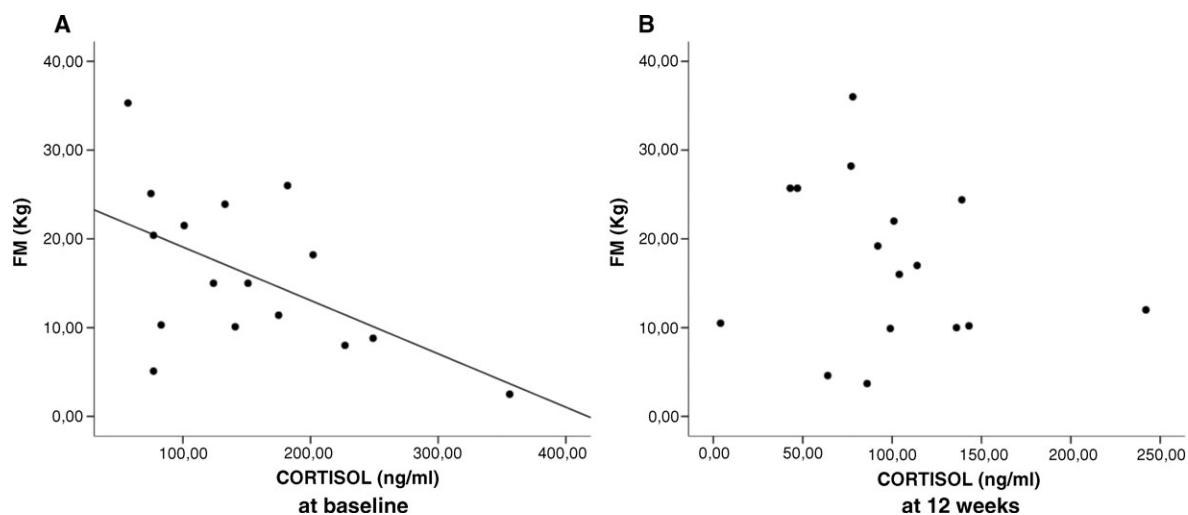


Fig. 1. Relationship between cortisol levels and fat mass (FM). At baseline, a significant inverse correlation was found between cortisol and FM [(a) $r = -0.54$, $P = 0.03$] while no correlation was found between cortisol and FM after 12 weeks of total alcohol abstinence [(b) $r = -0.18$, $P = 0.50$].

FM (Samra *et al.*, 1998). A state of hypercortisolemia was not present in our patients all showing cortisol levels within the normal range. However, within the normal values of cortisol, patients with higher cortisol levels showed lower FM values. In summary, in actively drinking alcoholics, a higher HPA-axis activation—reflected by higher cortisol levels—is associated with a lower FM, which reflects a more severe nutritional impairment. The correlation between FM and cortisol could reflect a possible relationship between HPA activation and hypermetabolism, as previously reported in different kinds of subjects (García-Prieto *et al.*, 2007). The results found in the present study are consistent with the role of the HPA axis in affecting energy balance and body composition (Nieuwenhuizen and Rutters, 2008). As a consequence, alterations in the HPA axis may induce an impairment of the body composition. In particular, alterations of the HPA axis have been described in subject with chronic alcohol abuse (Wand and Dobs, 1991; Costa *et al.*, 1996). Therefore, the impairment of the body composition present in active drinking alcoholics may recognize the alterations of the HPA axis as a factor, or at least as a cofactor.

A further consideration suggested by the present study is that a reduced hyperactivity of the HPA axis can play a role in the nutritional recovery of alcoholic patients after a period of total alcohol abstinence.

This hypothesis is supported by some results observed at 12 weeks of total alcohol abstinence in our patients, in particular: (i) the significant reduction of both cortisol and aldosterone; (ii) the significant increase of FM; and (iii) the disappearance of the correlation between cortisol and FM present at baseline. The reduced HPA activity is also in line with the parallel reduction of the hypermetabolism, the latter showed by the comparison between the baseline REE and baseline BMR and by the significant reduction of REE during abstinence (Székely and Szélenyi, 2005). In other words, the significant reduction of cortisol level and the disappearance of the correlation between cortisol and FM may represent a return of 'normal' metabolism in alcoholics after 3 months of total alcohol abstinence. Furthermore, the possibility that the subjects substituted food for alcohol during abstinence, thereby impacting their BMI and FM needs to be mentioned.

This study also showed a relationship between thyroid hormones and some nutritional parameters. A dysfunction of the thyroid gland and a possible interaction with the mood states in alcoholics has been extensively reported (for an extensive review, see Hermann *et al.*, 2002). Rather, this study included only alcoholics with thyroid hormones in the normal range and gave us the opportunity to explore the possible relationship between thyroid hormones and the nutritional parameters in alcoholics. In particular, the present study showed that both free-T3 and free-T4 correlate with FFM and TBW in the active-drinking phase. Free-T3 also correlated with FFM and TBW at 12 weeks of total abstinence. Taking into account that fat-free tissues are responsible for 95% of basal energy expenditure (Severi *et al.*, 2001), FFM is expected to be a better determinant of thyroid size and function than body weight (Wesche *et al.*, 1998). Accordingly, Sartorio *et al.* (2000) showed that in euthyroid healthy subjects, the thyroid function is more strongly associated with body impedance than anthropometry, suggesting that FFM may be a better 'denominator' for thyroid function than weight (Sartorio *et al.*, 2000). In summary, while there are no data in literature—to the best of our knowledge—

on this specific aspect in alcoholics, the relationship between thyroid hormones and FFM found in our euthyroid alcoholics and the lack of a correlation between thyroid hormones and both weight and BMI are in close agreement with the results found by Sartorio and colleagues (2000) in euthyroid healthy subjects. Therefore, our results suggest that FFM reflects the thyroid function, also in euthyroid alcoholic subjects.

It has been suggested that the preservation of FFM value in alcoholics does not necessarily imply a good maintenance of skeletal muscle mass, but it could be explained by an increase in the extracellular cellular water (ECW) component (Addolorato *et al.*, 1999). The increased ECW could derive from an increase in cellular permeability related to endothelial damage linked to the vasoconstriction present in the alcoholics and/or to a direct toxic effect of ethanol on cellular membranes (Addolorato *et al.*, 1999). The trend of increase of the NT-proBNP found in this study could reflect a reduction of the extracellular water as a compensatory effect during alcohol abstinence. This is consistent with the role of atrial peptides in the physiological response to plasma volume expansion (Ballermann and Brenner, 1986) and is supported by the inverse relationship between the NT-proBNP and TBW found in our patients. However, unfortunately this remains a speculation since we were not able to discern ECW from TBW.

This study has some limitations that need to be mentioned. First, the low number of patients enrolled limits the interpretability of the results and the analysis of possible cofactors (e.g. gender). Second, since chronic smoking can influence the nutritional status (Preston, 1991), the lack of a structured interview on the smoking habits could represent another limit. Third, we did not include a group of non-alcoholics to serve as healthy controls nor a group of alcoholics treated by placebo in order to exclude a possible influence of the anti-craving medication (baclofen). Another limit is the evaluation of TWB as an estimated function of the FFM, the latter calculated by DXA. However, it is also known that DXA provides an accurate assessment of FM (Falck-Ytter and McCullough, 2000), thereby strengthening the findings of decreased FM in our alcoholics. Finally, since the pilot nature of this study, we considered for analysis only those subjects totally abstinent after a follow-up period of 12 weeks. Moreover, we excluded subjects with endocrinological and/or metabolic alterations with the goal to study a homogeneous population but with the limit of a sample that prevents generalization of the results. Therefore, future studies will have to address possible differences between totally abstinent alcoholics and those relapsed during the follow-up and will also have to include a wider sample closer to the general population of alcoholics.

In conclusion, the present data expand the previous data on the presence of alterations of the body composition and nutritional status in alcoholics. This study also suggests a role of the HPA axis and in particular of cortisol in both the etiology of these alcohol-related alterations and their recovery after a period of total alcohol abstinence. This effect of alcohol abstinence on the nutritional impairment and on the HPA activity points out the importance of alcohol abstinence in the clinical management of alcoholics.

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